REQUEST FOR RECONSIDERATION

Clinically, recombinant human grown hormone (rhGH) is administered daily in growth hormone deficient patients. To decrease the dosing frequency and increase patient compliance sustained release formulations have been under development. These formulations have the potential to allow patients to decrease their dosing interval from daily to once or twice per month. The present invention addresses the release profile of sustained release formulations.

The present invention includes a sustained release composition including a carrier material containing a non-polymeric, non-water soluble liquid material having a viscosity of at least 5,000 cP at 37°C that does not crystallize neat under ambient physiological conditions, multivalent metal cations and growth hormone. This composition provides a very low burst of from 0.1 to 2.2% in 24 hours, followed by protein release over 28 days. A comparative composition, identical except for substitution of sodium bicarbonate for multivalent metal cations, gives a much higher initial burst, 7-14% in 24 hours.

The rejection of Claims 1 and 26-30 under 35 U.S.C. § 102 over European Patent Application 0 216 485 (EP '485) is respectfully traversed. None of the components used in the oil vehicles of EP '485, nor the oil vehicle itself, is a liquid material having a viscosity of at least 5,000 cP at 37°C.

EP '485 describes prolonged release of growth promoting hormones. This reference describes an oil vehicle together with an effective amount of a metal complex of a growth promoting hormone (page 2, lines 12-14). The oil vehicle is composed of 90-99% oil, and 1-10% of known adjuvants or excipients (page 4, lines 6-17). The oils include a variety of vegetable and mineral oils (page 3, line 35 to page 4, line 2). The adjuvants and excipients include beeswax, aluminum monostearate, carnauba, and paraffin (page 4, lines 11-15). These compositions are administered via injection or implants containing a pump or matrix (page 5, lines 22-35).

The present invention includes a liquid material having a viscosity of at least 5,000 cP at 37°C. The oils of the oil vehicle of EP '485 have viscosities far low than 5,000 cP at 37°C (see the attached page from "HANDBOOK OF CHEMISTRY AND PHYSICS", page 6-159, showing that the viscosity of olive oil and soybean oil to be less

than 100 cP at 20°C). The adjuvants and excipients of EP '485 are all solids. Finally, the mixture of the adjuvants or excipients, and the oils, are *injectable* compositions, and therefore must have relatively low viscosities. (Please note that the present invention includes a solvent with the liquid material having a viscosity of at least 5,000 cP at 37°C, in the examples where the composition is injected; Tipton et al. at column 6, lines 20-28, describes some of the unusual viscosity properties SAIB, a member of this class of liquid materials). Finally, there is no suggestion in EP '485 to use a liquid material having a viscosity of at least 5,000 cP at 37°C. Applicants submit that the claimed invention is neither anticipated by, nor obvious over, EP '485 alone.

The rejection of the claims under 35 U.S.C. § 103 over European Patent Application 0 216 485 (EP '485) in view of Tipton, et al. is respectfully traversed. The claimed invention provides for an initial burst which is about ten times smaller than comparative compositions which do not contain multivalent metal cations, a much lower initial burst than would have been expected based on the teachings of EP '485. These unexpected and superior results demonstrate the unobviousness of the claimed invention.

EP '485 is described above. Example 5 is the only example which compares the release rates of compositions which are identical except for the presence of multivalent metal cations (pages 10-14). In this example, compound 1 contains peanut oil, 5% aluminum monosterate and 8 mg/ml of uncomplexed Parlow swine grown hormone; formulation 3 contains peanut oil, 5% aluminum monosterate and 8 mg/ml of zinc complexed growth hormone (page 10, lines 23-31). Tables 4 and 5 (pages 12 and 13) show the serum growth hormone levels for administration of the two compositions over a period of time. The earliest point in time after administration of the growth hormone for which both examples have data is at the 24 hour mark: serum growth hormone was 84.6 ng/ml for the uncomplexed growth hormone, and 40.0 ng/ml for the complexed growth hormone. This shows a decrease in the amount released of about 50% when multivalent metal cations are present. This is consistent with the 200% increase in release time of the growth hormone as concluded by this reference (page 14, lines 13-18).

Tipton et al. has been cited for a description of SAIB. There is no discussion of changes in release rates of growth hormone from the presence or absence of multivalent metal cations.

The claimed invention shows a greater than 10 fold drop in amount of growth hormone released within the first 24 hours, as compared to compositions without multivalent metal cations. Figure 4 includes release rate data for comparable compositions which either contain multivalent metal cations, or sodium bicarbonate (this experiment is described in the specification, page 6, lines 11-25). In the ethanol containing composition, 0.53% of the multivalent metal cation containing composition was released in 24 hours, while the otherwise identical sodium bicarbonate composition released 6.53% over 24 hours. In the benzyl benzoate containing composition, 1.06% of the multivalent metal cation containing composition was released within 24 hours, while the sodium bicarbonate composition released 14.64% over 24 hours. This data indicates that the initial burst within 24 hours is reduced more than 10 fold when multivalent metal cations are present. Since EP '485 at best suggests a 2 fold decrease in initial burst within 24 hours, the present invention provides unexpected and superior results. Accordingly, Applicant submits that this data demonstrates the unobviousness of the claimed invention.

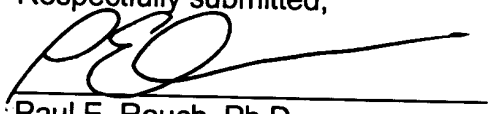
The objection to the drawings has been obviated by the filing herewith of formal drawings. Withdrawal of this objection is respectfully requested.

The objection to the abstract has been obviated by appropriate amendment.

The claim to priority has been corrected.

Applicant submits the application is now in condition for allowance. Early notice of such action is earnestly solicited.

Respectfully submitted,



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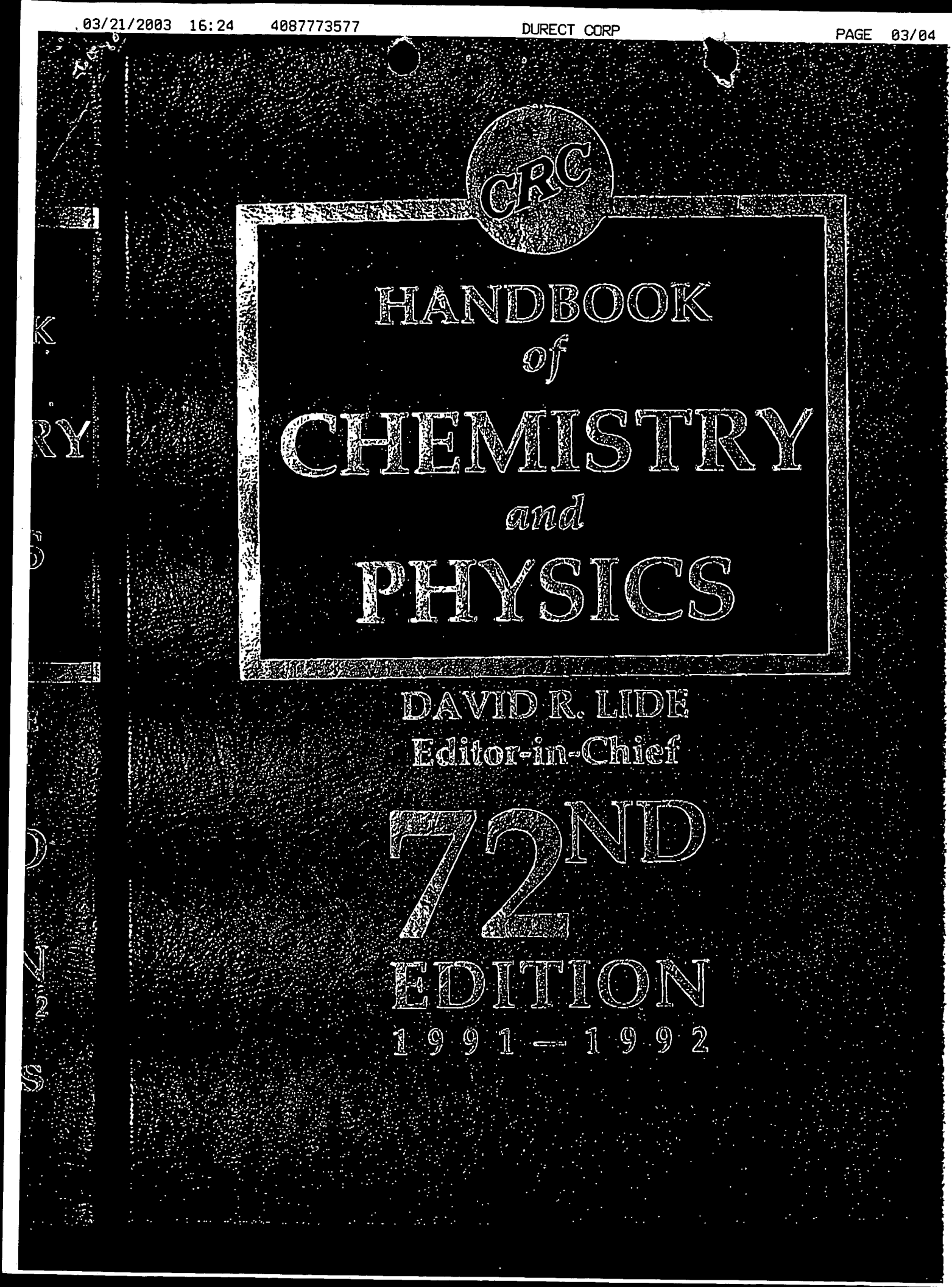
CRC
HANDBOOK
of
CHEMISTRY
and
PHYSICS
DAVID R. LIDE
Editor-in-Chief
72ND
EDITION
1991—1992

ap. C	Viscosity cp
15	2.86
30	1.77
25	3.57
25	3.031
50	2.68
100	2.32
141	2.116
500	1.84
551	1.70
600	1.38
703	1.349
844	1.165
55.6	6.20
74.6	2.47
90.0	1.04
−20	1.855
−10	1.764
0	1.685
10	1.615
19.02	1.56
20	1.554
20.2	1.55
30	1.499
40	1.450
40.8	1.45
41.86	1.44
50	1.407
60	1.367
70	1.331
80	1.298
90	1.268
100	1.240
150	1.130
200	1.052
250	.995
300	.950
340	.921
0	.484
20	.381
40	.320
−96.30	13.9
−84.23	6.8
−72.55	4.36
−44.63	1.98
−22.29	1.23
0	.82
15	.622
30	.597
25	.547
30	.510
40	.456
50	.403
0	.236
25	2.02
30	1.55
20	.1834
15	1.09
30	0.92
15	.449
30	.393
0	.606
15	.518
20	.500
20	.460
40	.424
80	.967
100	.776
0	2.275
10	1.770
2.95	2.91
5.69	2.71
6.94	2.71
9.92	2.45
14.04	2.24
20.00	2.03
0	.858
25	.620
0	2.83
20	2.37
40	1.03
60	1.21
20	2.33

VISCOSITY OF LIQUIDS (Continued)

Liquid	Temp. °C	Viscosity cp
	40	1.00
	60	1.18
p-Nitrotoluene	60	1.20
n-Nonane	20	.711
n-Octane	0	.706
	15	.574
	20	.542
	40	.433
tetodecane	40	2.88
n-Octylalcohol	15	10.6
Oil, castor	10	2,420
	20	986
	30	451
	40	231
	100	16.9
cottonseed	20	70.4
cylinder, filtered	37.8	240.6
	100	18.7
cylinder, dark	37.8	422.4
	100	24.0
linseed	30	33.1
	50	17.6
	90	7.1
machine, light	15.6	113.8
	37.8	34.2
	100	4.9
machine, heavy	15.6	660.6
	37.8	127.4
Oil, olive	10	138.0
	20	84.0
	40	38.3
	70	12.4
rape	0	2,540
	10	385
	20	163
	30	96
soya bean	20	69.3
	30	40.6
	50	20.6
	90	7.8
sperm	15.6	42.0
	37.8	18.5
	100.0	4.6
Oleic acid	30	25.6
Pentadecane	22	2.81
Pentane	0	.289
	20	.240
o-Phenetidine	0	16.5
	20	6.08
	30	4.22
m-Phenetidine	30	12.9
p-Phenetidine	20	12.9
	30	8.3
Phenol	18.3	12.7
	50	3.49
	60	2.61
	70	2.03
	90	1.25
Phenylcyanide	.26	1.96
	20.0	1.33
Phosphorus, liq	21.5	2.34
	31.2	2.01
	43.2	1.73
	50.5	1.60
	60.2	1.45
	69.7	1.32
	79.9	1.21
Potassium bromide, liq	742	1.48
	775	1.34
	905	1.19
nitrate, liq	334	2.1
	368	1.7
	333	2.97
	418	2.00
Propionic acid	10	1.289
	15	1.18
	20	1.102
	40	.845
Propyl acetate	10	.68
	20	.59
	40	.44

Liquid	Temp. °C	Viscosity cp
n-Propyl alcohol	0	3.853
	15	2.62
	20	2.256
	30	1.72
	40	1.405
n-Propyl alcohol	50	1.130
	70	.760
Propyl aldehyde	10	.47
	20	.41
	40	.33
bromide	0	.651
	20	.524
	40	.433
chloride	0	.426
	20	.352
	40	.291
n-Propyl ether	15	.448
Pyridine	20	.974
Salicylic acid	10	3.20
	20	2.71
	40	1.81
Salol	45	.746
Sodium bromide	762	1.42
	780	1.28
chloride, liq	841	1.20
	896	1.01
	924	.97
nitrate, liq	308	2.910
	348	2.439
	398	1.977
	418	1.828
Stearic acid	70	11.0
Sucrose (cane sugar)	100	2.8×10^8
	124.6	1.9×10^9
Sulfur (gas free)	123.0	10.94
	135.5	8.66
	142.6	7.09
	156.3	7.19
	158.2	7.59
	159.2	9.48
	159.5	14.42
	160.0	22.83
	160.3	77.32
	166.0	500.0
	171.0	4,500.0
	184.0	16,000.00
	190.5	19,700.0
	197.5	21,300.0
	200.0	21,500.0
	210.0	20,500.0
	217.0	19,100.0
	220.0	18,600.0
Sulfur dioxide, liq	−33.5	.3508
	−10.5	.4285
	0.1	.3936
Sulfuric acid	0	48.4
	15	32.8
	20	26.4
	30	15.7
	40	11.5
Sulfuric acid	50	8.82
	60	7.22
	70	6.09
	80	5.19
Tetrachloroethane	15	1.844
Tetradecane	20	2.14
Tin, liq	240	2.12
	280	1.678
	300	1.73
	301	1.680
	400	1.43
	450	1.270
	500	1.20
	600	1.08
	604	1.045
	750	.905
Toluene	0	.772
	17	.61
	20	.600
	30	.526
	40	.471